REMARKS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the remarks herewith. The Examiner is thanked for withdrawing the restriction requirement.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

Claims 67-96 are pending in the current application. Claims 69-76 and 83-86 have been withdrawn from further consideration. Claim 68 has been amended for clarity. Claims 67, 68 and 93 have been amended to replace the recitation "a compound lacking oestrogenic activity" with "a non-oestrogenic sulphamate compound" (support can be found in paragraphs 0014 and 0286 of the specification as published). Claims 88-91 and 94 have been amended to clarify the claim dependency. Claims 93 and 96 have been amended to end with a period. Claim 77 has been amended to correct the grammatical error. All amendments are made without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. No new matter has been added.

It is respectfully submitted that these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims and the remarks herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the amendments and remarks are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support for the amendments can be found throughout the specification and in the claims as originally filed.

II. THE REJECTIONS UNDER 35 U.S.C. §112 ARE OVERCOME

Claim 68, 78, 80, 82, 88, 90, 91, 93, and 94 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for all endocrine-dependent cancers. The rejection is respectfully traversed.

The Office Action states that the present specification provides data showing the anti-proliferative activity of the claimed compound in the breast cancer cells but it lacks data relating to the use of the claimed compound in other forms of cancer which may be "endocrine-dependent". The Office Action further asserts that the present specification also lacks description of "endocrine-dependent cancer" as well as guidance as to how one having ordinary

skill in the art would make the said determination. The Office Action concludes that one skilled in the art would first have to determine which cancers are "endocrine-dependent" by reviewing the prior art for definition of said cancers or for method(s) that would be useful in making such determination. Applicants respectfully disagree.

35 U.S.C. §112, first paragraph, requires that the specification describes how to make and use the invention. 35 U.S.C. §112, first paragraph, recites, in pertinent part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same[.]

A patent claim is invalid if it is not, *inter alia*, supported by an enabling disclosure. The test for enablement requires a determination of whether any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400, (Fed. Cir. 1988). The factors involved in determining whether there is sufficient evidence to support a finding of enablement include, among others, (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404.

The present claims relate to "a method for treating endocrine-dependent cancer comprising administering a non-oestrogenic sulphamate compound suitable for use as an inhibitor of oestrone sulphatase, to a patient in need of treatment of endocrine-dependent cancer by a compound lacking oestrogenic activity". Applicants respectfully submit that one skilled in the art would understand which cancers are endocrine-dependent. It is well known that endocrine system is a hormone producing system, and therefore tumors or cancers which develop in hormone-regulated organs such as breast, prostate, ovaries, etc., are called endocrine-dependent.

Steroid sulphatase is an enzyme that promotes growth of the tumors in hormone-regulated organs. Therefore a steroid sulphatase inhibitor can be used for treating the endocrine-dependent cancers.

The data presented in the current application clearly supports the claims to the treatment of breast tumors. Steroid sulphatase is present in breast cancer cells as well as in other cancer cells of endocrine-dependent (hormone-dependent) tissues. Accordingly, a person of skill in the art, having read and understood the present application, will understand that the present compounds are suitable for use in the treatment of other endocrine-dependent cancers.

Therefore, Applicants respectfully submit that the level of skill in the art is high, the level of guidance provided by the specification is high, working examples are present in the specification, the amount of experimentation is low given the teachings of the application, and the claims are of appropriate scope as they refer to endocrine-dependent cancers. Thus, Applicants respectfully submit that the pending claims are enabled.

Claim 68, 78, 80, 82, 88, and 90-96 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the invention at the time of filing. The rejection is respectfully traversed.

The Office Action asserts that the instant claims recite treating "endocrine-dependent cancer" and defines "breast, ovarian, endometrial and prostate cancers" as said endocrine-dependent cancers. The Office Action further alleges that the instant specification also defines breast cancer as "oestrone dependent tumor", but lacks definition of tumors that are endocrine-dependent. The Office Action further concludes that the claimed subject matter was not described in the present specification in such a way as to reasonably convey to the skilled artisan that Applicant, at the time the application was filed, had possession of the claimed invention. Applicants respectfully disagree.

Applicants respectfully reiterate that one skilled in the art would know that endocrine system is a hormone producing system, and therefore tumors or cancers which develop in hormone-regulated organs such as breast, prostate, ovaries, etc., are called endocrine-dependent.

The present specification defines breast cancer as "oestrone dependent tumor" because oestrone or estrone (estrogen) is a hormone secreted in adipose tissue (breast) which is an endocrine gland. Thus, the claimed subject matter can be easily understood by one skilled in the art.

The office action further contends that the present specification does not define "ovary" as an endocrine-dependent tissues. Applicants respectfully reiterate that one skilled in the art would know that ovaries are endocrine glands where several hormones including estrogens are secreted.

As such, based on the arguments presented above, Applicants respectfully submit that the claims of the present application are enabled by the specification and comply with the written description requirement.

Claim 67, 77, 79, 81, 87, 89, and 93-95 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The rejection is respectfully traversed.

The Office Action contends that the instant claims recite "a non-oestrogenic sulphamate compound suitable for use as an inhibitor of oestrone sulphatase to a patient in need of inhibition of steroid sulphatase activity by a compound *lacking* oestrogenic activity" while the specification defines "non-oestrogenic compound" as a compound exhibiting no or substantially no oestrogenic activity, so it does not differentiate between the instantly claimed compounds, and therefore, it does not reasonably convey to the skilled artisan in the art that Applicant, at the time the application was filed, had possession of the claimed invention. Applicants respectfully disagree.

Claims 67, 68 and 93 have been amended to replace the recitation "a compound lacking oestrogenic activity" with "a non-oestrogenic sulphamate compound" (support can be found in paragraphs 0014 and 0286 of the specification as published), thereby obviating a rejection. Furthermore, the phrase "a non-oestrogenic sulphamate compound" is recited in claim 96, which was not included in this rejection. Therefore the rejection is moot.

As such, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, are respectfully requested.

Claim 68, 78, 80, 82, 88, 93 and 96 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is respectfully traversed.

The Examiner alleges that the instant claims are indefinite for the following reasons:

a) Claims 68 and 93 recite treatment of "endocrine-dependent cancer", while the present specification lacks definition of cancers that are encompassed by the above-mentioned phrase.

b) Claim 88 recites a method "according to any of claims 68" and therefore requires correction.

c) Claims 93 and 96 lack a period and, thus, it is unclear where the claimed invention ends.

Applicants respectfully submit that the skilled artisan would be able to "determine the metes and bound" of the recitation of "endocrine-dependent cancer" of claims 68 and 93 as one skilled in the art would know that endocrine system is a hormone producing system, and therefore tumors or cancers which develop in hormone-regulated endocrine tissues such as breast, prostate, ovaries, etc., are called endocrine-dependent.

Claims 88, 93, and 96 have been amended thereby obviating the rejection.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph are respectfully requested.

III. THE DOUBLE PATENTING REJECTIONS ARE OVERCOME

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-4 and 7-10 of U.S. Patent No. 5, 616,574. The rejection is respectfully traversed.

The Examiner asserts that "the scope of the instantly claimed compounds is rendered obvious by the recitation of "substituted oestrone" and disclosure of "2-methoxy-oestrone" by the cited patent" and "that the methods of the pending claims "are rendered obvious by the disclosure of the cited patent that the prior art compounds inhibit steroid sulphatase activity and are useful in treating estrogen dependent tumors such as breast cancer". The Examiner further alleges that "similar compounds would have similar properties and, thus, 2-methoxy derivative taught by the reference would inherently lack oestrogenic activity".

Applicants respectfully submit that a finding of obviousness-type double patenting turns on whether the invention defined in a **claim** in the application in issue is an obvious variation of the invention defined in a **claim** in a prior patent. *See, e.g., In re Berg* , 46 U.S.P.Q.2d, 1226 (Fed. Cir. 1998). In order for an obviousness-type double patenting rejection to stand, the

Examiner must show that the claims in issue are obvious based **solely on the claims in the prior patent**; the disclosure in the prior patent may not be used as prior art. *See also In re Kaplan*, 229 U.S.P.Q. 678, 683 (Fed. Cir. 1986). Furthermore, any obvious-type double patenting rejection should make clear: (1) the differences defined by the conflicting claims; and, (2) the reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent. *See id.*

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate having at least one additional substituent at one or more of the 2- and 4-positions, whereas claims 1-4 and 7-10 of U.S. Patent No. 5,616,574 are drawn to a sulphamate ester of general formula (I) and a composition comprising the said compound. Therefore, based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound, including "substituted oestrone" with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and as a treatment for endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-4 and 7-10 of U.S. Patent No. 5,616, 574 would recognize that these are different inventions.

Contrary to the Examiner's assertion, the scope of the instantly claimed compounds is not obvious based on the recitation of "substituted oestrone" and "2-methoxy-oestrone" by the cited patent as the prior claims do not relate to the method comprising administering the specific substituted oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors to a patient in need of inhibition of steroid sulphatase activity by a compound with reduced oestrogenicity.

Applicants previously submitted a copy of Purohit *et al.* "The Development of A-ring Modified Analogues of Oestrone-3-O-sulphamate as Potent Steroid Sulphatase Inhibitors with

Reduced Oestrogenicity", published in 1998. As described in Purohit, one of the problems in the art surround the use of standard steroid sulphatase inhibitors such as EMATE is that the compounds have a stimulatory effect on uterine growth. Such a stimulatory effect is undesirable in potential therapies for diseases such as cancer.

Surprisingly, it has now been found that the A-ring modified compounds of the present invention, having at least one additional substituent at one or more of the 2- and 4-positions, are vastly superior to previous steroid sulphatase inhibitors. Specifically, the A-ring modified compounds exhibit steroid sulphatase inhibition with significantly decreased estrogenicity when compared to compounds such as EMATE. For example, the Examiner's attention is respectfully directed to Figure 4 of Purohit *et al.*, which compares *in vivo* sulphatase activity following administration of 2- or 4-position substituted derivates or EMATE. The sulphatase activity measured following administration of compounds such as 4-Nitro EMATE, 2-Methoxy EMATE, and 4-n-Propyl EMATE was statistically similar to the activity levels measured following administration of EMATE. Furthermore, Figure 5 of Purohit *et al.* depicts the results of the uterine growth assay, which demonstrates that administration of A-ring derivate compounds resulted in little or no uterine growth, in contrast to the effects of the administration of EMATE.

Furthermore, Applicants previously submitted a reference by Jordan describing a sub-population of patients for which the non-oestrogenic sulphatase inhibitors of the present invention would be indicated.

Applicants respectfully submit that "substituted oestrone" derivatives taught by the reference would not inherently lack oestrogenic activity.

It is not enough for one to contend that the compounds in the relied-upon reference would "inherently" speak to the instantly claimed invention. The references must disclose or suggest the properties for inherency to attach. According to *In re Rijckaert*, 9 F.3d 1531, 1957 (Fed. Cir. 1993), "such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." The Federal Circuit is clear that "'inherency...may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].'" *Continental Can Company v. Monsanto Company*, 948 F.2d 1264, 1269 (Fed. Cir. 1991), *citing to In re Oelrich*, 666 F.2d 578, 581-582 (C.C.P.A. 1981). Indeed, "before a reference can be found to disclose a feature by virtue of its inherency, one of ordinary skill in the art viewing the reference must understand that

the unmentioned feature at issue is *necessarily* present in the reference." *SGS-Thomson Microelectronics, Inc. v. International Rectifier Corporation*, 31 F.3d 1177 (Fed. Cir. 1994) (emphasis in original). Applying the law to the instant facts, the cited reference does not inherently disclose or suggest Applicants' invention. That is, the reference does not inherently teach, disclose or suggest that **any** "substituted oestrone" is superior to previous steroid sulphatase inhibitors and exhibits steroid sulphatase inhibition with significantly decreased estrogenicity. The reference does not teach or suggest that the specific substituted oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, can be administered as potent non-oestrogenic steroid sulphatase inhibitors to a patient in need of inhibition of steroid sulphatase activity by a compound with reduced oestrogenicity.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-9 of U.S. Patent No. 5,830,886. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate, whereas claims 1-9 of U.S. Patent No. 5,830,886 are drawn to the methods of inhibiting steroid sulphatase activity comprising administering a ring system compound which comprises a polycyclic ring to which is attached a sulphamate group. Therefore, based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound, including "substituted oestrone" with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and as a treatment for endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-9 of U.S. Patent No. 5,830,886 would recognize that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic oestrone-3-sulphamate derivatives having at least one additional substituent at one or more of the 2- and 4-positions which inhibit steroid sulphatase with significantly decreased estrogenicity. Moreover, the prior **claims** do not disclose 2-methoxy substituted oestrone sulphamate as they do not teach or suggest any additional modifications of the A-ring of the previously disclosed oestrone sulphamates.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-5 of U.S. Patent No. 6,011,024. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate having at least one additional substituent at one or more of the 2- and 4-positions in patients in need of inhibition of steroid sulphatase activity by a compound with reduced oestrogenicity, whereas claims 1-5 of U.S. Patent No. 6,011,024 are drawn to the methods of inhibiting steroid sulphatase activity comprising administering a ring system compound which comprises a steroidal or non-steroidal ring system and a sulphamate group and wherein said compound is an inhibitor of an enzyme having steroid sulphatase activity (EC 3.1.6.2); and wherein when the sulphamate group of said compound is replaced with a sulphate group to form a sulphate compound and incubated with a steroid

sulphatase enzyme (EC 3.1.6.2) at a pH of 7.4 and 37° C. it provides a K_m, value of less than 50 μM. Therefore, based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and as a treatment for endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-5 of U.S. Patent No. 6,011,024 would recognize that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. Moreover, the prior claims do not disclose 2-methoxy substituted oestrone sulphamate as they do not teach or suggest any additional modifications of the A-ring of the previously disclosed oestrone sulphamates.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-8 of U.S. Patent No. 6,159,960. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate having at least one additional substituent at one or more of the 2- and 4-positions, whereas claims 1-8 of U.S. Patent No. 6,159,960 are drawn to the methods of inhibiting steroid sulphatase activity comprising administering a ring system compound having a sulphamic acid ester group; wherein said compound is an inhibitor of

an enzyme having steroid sulphatase activity (EC 3.1.6.2); and wherein when the sulphamic acid ester group of said compound is replaced with a sulphate group to form a sulphate compound and incubated with a steroid sulphatase enzyme (EC 3.1.6.2) at a pH 7.4 and 37° C. it provides a K_m, value of less than 50 μM. Therefore, based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and as a treatment for endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-8 of U.S. Patent No. 6,159,960 would recognize that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. Moreover, the prior claims do not disclose 2-methoxy substituted oestrone sulphamate as they do not teach or suggest any additional modifications of the A-ring of the previously disclosed oestrone sulphamates.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-3 of U.S. Patent No. 6,187,766. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate having at least one additional substituent at one or more of the 2- and 4-positions, whereas claims 1-3 of U.S. Patent No. 6,187,766 are

drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a ring system compound present in an amount to provide 100-500 mg of compound per unit dose; wherein the ring system compound has a ring system and a sulphamate group; wherein said compound is an inhibitor of an enzyme having steroid sulphatase activity (EC 3.1.6.2); and wherein when the sulphamate group of said compound is replaced with a sulphate group to form a sulphate compound it provides a substrate for a steroid sulphatase enzyme (EC 3.1.6.2); and wherein when the sulphamate group of said compound is replaced with a sulphate group to form a sulphate compound and incubated with a steroid sulphatase enzyme (EC 3.1.6.2) at a pH 7.4 and 37° C. it provides a K_m, value of less than 50 μM. Therefore, based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and for treating endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-3 of U.S. Patent No. 6,187,766 would recognize that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. Moreover, the prior claims do not disclose 2-methoxy substituted oestrone sulphamate as they do not teach or suggest any additional modifications of the A-ring of the previously disclosed oestrone sulphamates.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-3 and 8-13 of U.S. Patent No. 6,476,011. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate having at least one additional substituent at one or more of the 2- and 4-positions, whereas claims 1-3 and 8-13 of U.S. Patent No. 6,476,011 are drawn to a method for introducing an estrogenic compound into a subject in need thereof comprising administering an effective amount of a ring system compound having the formula (II) and the ring system ABCD represents a substituted or unsubstituted, saturated or unsaturated steroid nucleus selected from the group consisting of oestrones, dehydroepiandrosterones, substituted oestrones, oestradiols, substituted oestradiols, oestriols, substituted dehydroepiandrosterones and substituted oestriols; wherein said compound is an inhibitor of an enzyme having steroid sulphatase activity (EC 3.1.6.2), or a pharmaceutically acceptable salt thereof. Therefore, based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and for treating endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-3 and 8-13 of U.S. Patent No. 6,476,011 would recognize that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. The prior claims do not disclose a method of inhibiting steroid sulphatase activity comprising administering a non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate compound and a method of treating endocrine-dependent cancer comprising administering the said non-oestrogenic oestrone derivative.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-12 and 15-17 of U.S. Patent No. 6,642,397. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate having at least one additional substituent at one or more of the 2- and 4-positions, whereas claims 1-12 and 15-17 of U.S. Patent No. 6,642,397 are drawn to a purified compound wherein the polycyclic group is a ring system comprising at least four rings, at least three of which are fused; wherein the compound is an inhibitor of an enzyme having steroid sulphatase activity (E.C.3.1.6.2); wherein if the sulphamate group on the compound were to be replaced with a sulphate group to form a sulphate compound and incubated with a steroid sulphatase enzyme (E.C.3.1.6.2) at a pH 7.4 and 37° C. it would provide a K_m, value of less than 50 μM. Therefore, based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and for treating endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-12 and 15-17 of U.S. Patent No. 6,642,397 would recognize that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. Moreover, the prior claims do not disclose

2-methoxy substituted oestrone sulphamate as they do not teach or suggest any specific modifications of the A-ring of the previously disclosed oestrone sulphamates.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-8 and 10-14 of U.S. Patent No. 6,676,934. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate". The Examiner further alleges that "similar compounds would have similar properties and, thus, 2-methoxy-EMATE taught by the reference would inherently lack oestrogenic activity".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate having at least one additional substituent at one or more of the 2- and 4-positions, whereas claims 1-8 and 10-14 of U.S. Patent No. 6,676,934 are drawn to a composition comprising a polycyclic sulphamate compound comprising a sulphamate group or a pharmaceutically acceptable salt thereof and wherein the polycyclic sulphamate compound or pharmaceutically acceptable salt thereof inhibits steroid sulphatase and disrupts microtubules; **and** a biological response modifier such as a tumor necrosis factor alpha (TNF-α). Therefore, based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and for treating endocrine-dependent cancer as taught by the pending claims.

Contrary to the Examiner's assertion, the scope of the instantly claimed compounds is not obvious based on the recitation of a single compound, 2-methoxy-oestrone, by the cited patent as the prior claims do not relate to the method comprising administering the non-oestrogenic specifically substituted oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be

both H, as potent non-oestrogenic steroid sulphatase inhibitors to a patient in need of inhibition of steroid sulphatase activity by a compound with reduced oestrogenicity.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-8 and 10-14 of U.S. Patent No. 6,676,934 would recognize that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic oestrone-3-sulphamate derivatives having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors. Moreover, the prior claims do not relate to the method comprising administering the non-oestrogenic compounds to a patient in need of inhibition of steroid sulphatase activity by a compound with reduced oestrogenicity.

Furthermore, as the prior claims relate to a composition comprising a polycyclic sulphamate compound comprising a sulphamate group or a pharmaceutically acceptable salt thereof and wherein the polycyclic sulphamate compound or pharmaceutically acceptable salt thereof inhibits steroid sulphatase and disrupts microtubules; **and** a biological response modifier such as a tumor necrosis factor alpha (TNF-α), one skilled in the art would not be able to predict that such compositions comprising a biological response modifier in addition to the sulphamate compound could be administered to a patient in need of inhibition of steroid sulphatase activity by a compound with reduced oestrogenicity. Moreover, the granted claims provide no motivation to administer the described compounds without the biological response modifier to a patient in need of treatment by a compound with reduced oestrogenicity.

Applicants respectfully submit that by reciting "*2-methoxy-EMATE*" as an example of a polycyclic sulphamate compound comprising a sulphamate group, the reference does not teach or suggest that all polycyclic sulphamate compounds are inherently non-oestrogenic and does not motivate the one skilled in the art to use other substituted oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors.

It is not enough for one to contend that the compounds in the relied-upon reference would "inherently" speak to the instantly claimed invention. The references must disclose or suggest the properties for inherency to attach. According to *In re Rijckaert*, 9 F.3d 1531, 1957 (Fed. Cir. 1993), "such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." The Federal Circuit is clear that "'inherency...may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].'" *Continental Can Company v. Monsanto Company*, 948 F.2d 1264, 1269 (Fed. Cir. 1991), *citing to In re Oelrich*, 666 F.2d 578, 581-582 (C.C.P.A. 1981). Indeed, "before a reference can be found to disclose a feature by virtue of its inherency, one of ordinary skill in the art viewing the reference must understand that the unmentioned feature at issue is *necessarily* present in the reference." *SGS-Thomson Microelectronics, Inc. v. International Rectifier Corporation*, 31 F.3d 1177 (Fed. Cir. 1994) (emphasis in original). Applying the law to the instant facts, the cited reference does not inherently disclose or suggest Applicants' invention. That is, the reference does not inherently teach, disclose or suggest that the specifically substituted sulphatase inhibitors of the present claims inhibit steroid sulphatase with significantly decreased estrogenicity.

As the granted claims of the reference patent do not mention or suggest that the compounds they encompass are non-oestrogenic, they cannot inherently relate to such a property; especially given the fact that inherency must be inevitable, not merely possible or probable.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-12 and 20 of U.S. Patent No. 6,677,325. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate". The Examiner further alleges that "similar compounds would have

similar properties and, thus, 2-methoxy-EMATE taught by the reference would inherently lack oestrogenic activity".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors to a patient in need of inhibition of steroid sulphatase by a non-oestrogenic compound, whereas claims 1-12 and 20 of U.S. Patent No. 6,677,325 are drawn to a method for inhibiting estrone or estradiol production, or both, in a subject in need thereof comprising administering a ring system compound comprising a sulfamic ester group and the ring system ABCD represents a substituted or unsubstituted, saturated or unsaturated steroid nucleus, selected from the group consisting of oestrones, dehydroepiandrosterone, substituted oestrones, oestradiols, substituted oestradiols, oestriols or substituted oestriols; wherein said compound is an inhibitor of an enzyme having steroid sulphatase activity (EC 3.1.6.2), or a pharmaceutically acceptable salt thereof. Therefore, based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and for treating endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-12 and 20 of U.S. Patent No. 6,677,325 would recognize that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. The prior claims do not disclose a method of inhibiting steroid sulphatase activity comprising administering a non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate compound and a method of treating endocrine-dependent cancer comprising administering the said non-oestrogenic oestrone derivative.

Applicants respectfully submit that by reciting "*2-methoxy-EMATE*" as an example of a sulphamate compound of formula (II), the reference does not teach or suggest that all sulphamate compounds of formula (II) are inherently non-oestrogenic and does not motivate the one skilled in the art to use the substituted oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors.

It is not enough for one to contend that the compounds in the relied-upon reference would "inherently" speak to the instantly claimed invention. The references must disclose or suggest the properties for inherency to attach. According to *In re Rijckaert*, 9 F.3d 1531, 1957 (Fed. Cir. 1993), "such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." The Federal Circuit is clear that "'inherency...may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].'" *Continental Can Company v. Monsanto Company*, 948 F.2d 1264, 1269 (Fed. Cir. 1991), *citing to In re Oelrich*, 666 F.2d 578, 581-582 (C.C.P.A. 1981). Indeed, "before a reference can be found to disclose a feature by virtue of its inherency, one of ordinary skill in the art viewing the reference must understand that the unmentioned feature at issue is *necessarily* present in the reference." *SGS-Thomson Microelectronics, Inc. v. International Rectifier Corporation*, 31 F.3d 1177 (Fed. Cir. 1994) (emphasis in original). Applying the law to the instant facts, the cited reference does not inherently disclose or suggest Applicants' invention. That is, the reference does not inherently teach, disclose or suggest that the specifically substituted sulphatase inhibitors of the present claims inhibit steroid sulphatase with significantly decreased estrogenicity.

As the granted claims of the reference patent do not mention or suggest that the compounds they encompass are non-oestrogenic, they cannot inherently relate to such a property; especially given the fact that inherency must be inevitable, not merely possible or probable.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-48 of U.S. Patent No. 6,903,084. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors to a patient in need of inhibition of steroid sulphatase by a non-oestrogenic compound, whereas claims 1-48 of U.S. Patent No. 6,903,084 are drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a pharmaceutically effective amount of a compound of the formula (II) and the ring system ABCD represents a steroid nucleus, selected from the group consisting of dehydroepiandrosterone, oestrone, 2-OH-oestrone, 7α-OH-oestrone, 2-methoxy-oestrone, 16α-OH-oestrone, 4-OH-oestrone, 16β-OH-oestrone, 6α-OH-oestrone, 2-OH-17β-oestradiol, 6α-OH-17β-oestradiol, 16β-OH-7α-oestradiol, 17β-oestradiol, 2-methoxy-17β-oestradiol, 7α-OH-17β-oestradiol, 16α-OH-17α-oestradiol, 17α-ethinyl-17~-oestradiol, 4-OH-17β-oestradiol, 16α-OH-17α-oestradiol, 17α-oestradiol, oestradiol, 4-OH-oestradiol, 2-OH-oestradiol, 6α-OH-oestradiol, 2-methoxy-oestradiol, 7α-OH-oestradiol, 6α-OH-dehydroepiandrosterone, 16α-OH-dehydroepiandrosterone, 7α-OHdehydroepiandrosterone, and 16β-OHdehydroepiandrosterone, wherein said compound is an inhibitor of an enzyme having steroid sulphatase activity (EC 3.1.6.2); and wherein when the sulphamic acid ester group of said compound is replaced with a sulphate group to form a sulphate compound and incubated with a steroid sulphatase enzyme (EC 3.1.6.2) at a pH 7.4 and 37° C. it provides a K_m, value of less than 50 μM, or a pharmaceutically acceptable salt thereof. Based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize the prior compounds with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and for treating endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-48 of U.S. Patent No. 6,903,084 would recognize that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. The prior claims do not disclose a method of inhibiting steroid sulphatase activity comprising administering a non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate compound and a method of treating endocrine-dependent cancer comprising administering the said non-oestrogenic oestrone derivative.

Applicants respectfully submit that "substituted oestrone" derivatives, including 2-methoxy-emate, taught by the reference would not inherently lack oestrogenic activity.

It is not enough for one to contend that the compounds in the relied-upon reference would "inherently" speak to the instantly claimed invention. The references must disclose or suggest the properties for inherency to attach. According to *In re Rijckaert*, 9 F.3d 1531, 1957 (Fed. Cir. 1993), "such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." The Federal Circuit is clear that "'inherency...may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].'" *Continental Can Company v. Monsanto Company*, 948 F.2d 1264, 1269 (Fed. Cir. 1991), *citing to In re Oelrich*, 666 F.2d 578, 581-582 (C.C.P.A. 1981). Indeed, "before a reference can be found to disclose a feature by virtue of its inherency, one of ordinary skill in the art viewing the reference must understand that the unmentioned feature at issue is *necessarily* present in the reference." *SGS-Thomson Microelectronics, Inc. v. International Rectifier Corporation*, 31 F.3d 1177 (Fed. Cir. 1994) (emphasis in original). Applying the law to the instant facts, the cited reference does not inherently disclose or suggest Applicants' invention. That is, the reference does not inherently teach, disclose or suggest that the prior "substituted oestrone" is superior to previous steroid sulphatase inhibitors and exhibits steroid sulphatase inhibition with significantly decreased estrogenicity.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-4 and 9-27 of U.S. Patent No. 7,067,503. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate". The Examiner further alleges that "similar compounds would have similar properties and, thus, 2-methoxy-EMATE taught by the reference would inherently lack oestrogenic activity".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors to a patient in need of inhibition of steroid sulphatase by a non-oestrogenic compound, whereas claims 1-4 and 9-27 of U.S. Patent No. 7,067,503 are drawn to a compound of formula IV wherein R^1 is selected from anyone of a sulphamate group, a phosphonate group, a thiophosphonate group, a sulphonate group or a sulphonamide group; wherein group R^2 is of the formula L-R^3, wherein L is an optional linker group and R^3 is an aromatic hydrocarbyl group, and wherein the A ring of the steroidal ring system is substituted with a group R^4, wherein R^4 is a hydrocarbyl group. Based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and for treating endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-4 and 9-27 of U.S. Patent No. 7,067,503 would recognize

that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. The prior claims do not disclose a method of inhibiting steroid sulphatase activity comprising administering a non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate compound and a method of treating endocrine-dependent cancer comprising administering the said non-oestrogenic oestrone derivative.

Applicants respectfully submit that by reciting "*2-methoxy-EMATE*" as an example of a sulphamate compound of formula (IV), the reference does not teach or suggest that all sulphamate compounds of formula (IV) are inherently non-oestrogenic and does not motivate the one skilled in the art to use the substituted oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors.

It is not enough for one to contend that the compounds in the relied-upon reference would "inherently" speak to the instantly claimed invention. The references must disclose or suggest the properties for inherency to attach. According to *In re Rijckaert*, 9 F.3d 1531, 1957 (Fed. Cir. 1993), "such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." The Federal Circuit is clear that "'inherency...may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].'" *Continental Can Company v. Monsanto Company*, 948 F.2d 1264, 1269 (Fed. Cir. 1991), *citing to In re Oelrich*, 666 F.2d 578, 581-582 (C.C.P.A. 1981). Indeed, "before a reference can be found to disclose a feature by virtue of its inherency, one of ordinary skill in the art viewing the reference must understand that the unmentioned feature at issue is *necessarily* present in the reference." *SGS-Thomson Microelectronics, Inc. v. International Rectifier Corporation*, 31 F.3d 1177 (Fed. Cir. 1994) (emphasis in original). Applying the law to the instant facts, the cited reference does not inherently disclose or suggest Applicants' invention. That is, the reference does not inherently teach, disclose or suggest that the specifically substituted sulphatase inhibitors of the present claims inhibit steroid sulphatase with significantly decreased estrogenicity.

As the granted claims of the reference patent do not mention or suggest that the compounds they encompass are non-oestrogenic, they cannot inherently relate to such a

property; especially given the fact that inherency must be inevitable, not merely possible or probable.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-4, 6, 7, 9-24 and 26-31 of U.S. Patent No. 7,078,395. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors to a patient in need of inhibition of steroid sulphatase by a non-oestrogenic compound, whereas claims 1-4, 6, 7, 9-24 and 26-31 of U.S. Patent No. 7,078,395 are drawn a method of treating a cancer, in a subject in need thereof; wherein said cancer is hormone independent and wherein said cancer is susceptible to being treated by inhibition or arresting of cell cycling, by a cyclic compound or pharmaceutically active salt thereof, said method comprising inhibiting or arresting cell cycling by the cyclic compound or pharmaceutically active salt thereof by administering to said subject, the cyclic compound or a pharmaceutically active salt thereof in an amount sufficient to, inhibit or arrest cell cycling and thus treat the cancer susceptible to being treated, inhibition or arresting of cell cycling by the cyclic compound or pharmaceutically active salt thereof, wherein the cyclic compound comprises a polycyclic ring structure to which is attached a Group I and a Group II, independently of each other, wherein the polycyclic ring structure has the formula, wherein each ring A, B, C and D of ring system ABCD is optionally independently further substituted or unsubstituted, saturated or unsaturated; and wherein Group I is a hydrocarbyl or an oxyhydrocarbyl group; and wherein Group II is a group of the formula, wherein each of R_1 and

R_2 is independently selected from H or alkyl, cycloalkyl, alkenyl, or aryl, or together represent alkylene, which optionally contain one or more hereto atoms.

Based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and for treating endocrine-dependent cancer in a patient in need of inhibition of steroid sulphatase by a non-oestrogenic compound as taught by the pending claims. Contrary to the Examiner's assertion, claim 31 does not relate to any specific compounds as being non-oestrogenic.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-4, 6, 7, 9-24 and 26-31 of U.S. Patent No. 7,078,395 would recognize that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. The prior claims do not disclose a method of inhibiting steroid sulphatase activity comprising administering a non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate compound and a method of treating endocrine-dependent cancer comprising administering the said non-oestrogenic oestrone derivative.

Moreover, Applicants would like to reiterate that the granted claims of the reference patent relate to the treatment of hormone independent cancers by arresting cell cycling. Therefore, these claims do not relate to the methods comprising administering non-oestrogenic compounds of the present claims to a patient in need of treatment of endocrine-dependent cancer by a non-oestrogenic compound. The granted claims do not explicitly mention that steroid sulphatase inhibition *per se* forms part of the compounds' action against hormone-independent cancers.

Applicants respectfully submit that by reciting "*2-methoxy-EMATE*" as an example of a cyclic compound, the reference does not teach or suggest that all cyclic compounds described are inherently non-oestrogenic and does not motivate the one skilled in the art to use the substituted oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2-

and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors.

It is not enough for one to contend that the compounds in the relied-upon reference would "inherently" speak to the instantly claimed invention. The references must disclose or suggest the properties for inherency to attach. According to *In re Rijckaert*, 9 F.3d 1531, 1957 (Fed. Cir. 1993), "such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." The Federal Circuit is clear that "'inherency...may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].'" *Continental Can Company v. Monsanto Company*, 948 F.2d 1264, 1269 (Fed. Cir. 1991), *citing to In re Oelrich*, 666 F.2d 578, 581-582 (C.C.P.A. 1981). Indeed, "before a reference can be found to disclose a feature by virtue of its inherency, one of ordinary skill in the art viewing the reference must understand that the unmentioned feature at issue is *necessarily* present in the reference." *SGS-Thomson Microelectronics, Inc. v. International Rectifier Corporation*, 31 F.3d 1177 (Fed. Cir. 1994) (emphasis in original). Applying the law to the instant facts, the cited reference does not inherently disclose or suggest Applicants' invention. That is, the reference does not inherently teach, disclose or suggest that the specifically substituted sulphatase inhibitors of the present claims inhibit steroid sulphatase with significantly decreased estrogenicity.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-8 of U.S. Patent No. 7,098,199. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate compounds having at least one other

substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors to a patient in need of inhibition of steroid sulphatase by a non-oestrogenic compound, whereas claims 1-8 of U.S. Patent No. 7,098,199 are drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound comprising a steroidal ring structure and a sulphamate group, wherein the compound is an inhibitor of an enzyme having steroid sulphatase activity (E.C.3.1.6.2); wherein if the sulphamate group on the compound were to be replaced with a sulphate group to form a sulphate compound and incubated with a steroid sulphatase enzyme (E.C.3.1.6.2) at a pH 7.4 and 37° C. it would provide a K_m value of less than 50 μM. . Based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and for treating endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-8 of U.S. Patent No. 7,098,199 would recognize that these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. The prior claims do not disclose a method of inhibiting steroid sulphatase activity comprising administering a non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate compound and a method of treating endocrine-dependent cancer comprising administering the said non-oestrogenic oestrone derivative.

Contrary to the Examiner's assertion, the scope of the instantly claimed compounds is not obvious based on the recitation of "substituted oestrone" by the cited patent as the prior claims do not relate to the method comprising administering the specific substituted oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors to a patient in need of inhibition of steroid sulphatase activity by a compound with reduced oestrogenicity.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-4 and 8-11 of U.S. Patent No. 7,119,081. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate". The Examiner further alleges that "similar compounds would have similar properties and, thus, 2-methoxy-EMATE taught by the reference would inherently lack oestrogenic activity".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors to a patient in need of inhibition of steroid sulphatase by a non-oestrogenic compound, whereas claims 1-8 of U.S. Patent No. 7,098,199 are drawn to a compound of formula (Iva) wherein R^1 and R^2 are sulphamate groups, wherein each sulphamate group is independently selected from sulphamate groups of the formula, wherein each of R^4 and R^5 is independently selected from H and hydrocarbyl; and wherein R^3 is a hydrocarbyl or oxyhydrocarbyl group. Based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and for treating endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-4 and 8-11 of U.S. Patent No. 7,119,081 would recognize that

these are different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. The prior claims do not disclose a method of inhibiting steroid sulphatase activity comprising administering a non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate compound and a method of treating endocrine-dependent cancer comprising administering the said non-oestrogenic oestrone derivative.

Applicants respectfully submit that by reciting "*2-methoxy-EMATE*" as an example of a sulphamate compound of formula (IVa), the reference does not teach or suggest that all sulphamate compounds of formula (IVa) are inherently non-oestrogenic and does not motivate the one skilled in the art to use the substituted oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors.

It is not enough for one to contend that the compounds in the relied-upon reference would "inherently" speak to the instantly claimed invention. The references must disclose or suggest the properties for inherency to attach. According to *In re Rijckaert*, 9 F.3d 1531, 1957 (Fed. Cir. 1993), "such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." The Federal Circuit is clear that "'inherency...may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].'" *Continental Can Company v. Monsanto Company*, 948 F.2d 1264, 1269 (Fed. Cir. 1991), *citing to In re Oelrich*, 666 F.2d 578, 581-582 (C.C.P.A. 1981). Indeed, "before a reference can be found to disclose a feature by virtue of its inherency, one of ordinary skill in the art viewing the reference must understand that the unmentioned feature at issue is *necessarily* present in the reference." *SGS-Thomson Microelectronics, Inc. v. International Rectifier Corporation*, 31 F.3d 1177 (Fed. Cir. 1994) (emphasis in original). Applying the law to the instant facts, the cited reference does not inherently disclose or suggest Applicants' invention. That is, the reference does not inherently teach, disclose or suggest that the specifically substituted sulphatase inhibitors of the present claims inhibit steroid sulphatase with significantly decreased estrogenicity.

As the granted claims of the reference patent do not mention or suggest that the compounds they encompass are non-oestrogenic, they cannot inherently relate to such a

property; especially given the fact that inherency must be inevitable, not merely possible or probable.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-16 of U.S. Patent No. 7,211,246. The rejection is respectfully traversed.

The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass 2-methoxy substituted oestrone sulphamate".

Claims 67, 68, 77-82 and 87-96 of the present application are drawn to the methods of inhibiting steroid sulphatase activity and treating endocrine-dependent cancer comprising administering a non-oestrogenic oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors to a patient in need of inhibition of steroid sulphatase by a non-oestrogenic compound, whereas claims 1-16 of U.S. Patent No. 7,211,246 are drawn to a composition comprising a sulphamate compound, wherein an (oxy)hydrocarbyl group is attached to the 2 position of the A ring of the steroidal structure; **and** an apoptosis inducer, wherein the apoptosis inducer is a tumor necrosis factor-related apoptosis inducing ligand that binds to TRAIL-RI or TRAIL-R2. Based solely on the claims of the prior patent, it would not be obvious to one skilled in the art to utilize **any** prior compound with the reasonable expectation that the prior claimed compound would be useful as a non-oestrogenic inhibitor of steroid sulphatase and for treating endocrine-dependent cancer as taught by the pending claims.

Applicants respectfully reiterate that obviousness-type double patenting differs from the test of obviousness in that only the claims are compared to the exclusion of looking to the specification or other prior art sources to address any differences between the claims. As such, one of ordinary skill in the art when confronted only with claims 67, 68, 77-82 and 87-96 of the present invention and claims 1-16 of U.S. Patent No. 7,211,246 would recognize that these are

different inventions. The prior claims do not relate to the presently disclosed non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate derivatives which inhibit steroid sulphatase with significantly decreased estrogenicity. The prior claims do not disclose a method of inhibiting steroid sulphatase activity comprising administering a non-oestrogenic 2- and 4-substituted oestrone-3-sulphamate compound and a method of treating endocrine-dependent cancer comprising administering the said non-oestrogenic oestrone derivative.
Furthermore, as the prior claims relate to a composition comprising a sulphamate compound, wherein an (oxy)hydrocarbyl group is attached to the 2 position of the A ring of the steroidal structure; **and** an apoptosis inducer, wherein the apoptosis inducer is a tumor necrosis factor-related apoptosis inducing ligand that binds to TRAIL-RI or TRAIL-R2, one skilled in the art would not be able to predict that such compositions comprising a biological response modifier in addition to the sulphamate compound could be administered to a patient in need of inhibition of steroid sulphatase activity by a compound with reduced oestrogenicity.

Furthermore, the granted claims provide no motivation to administer the described compounds without the biological response modifier to a patient in need of treatment by a compound with reduced oestrogenicity.

As such, the present claims are patentably distinct from the claims of the cited patent.

Accordingly, reconsideration and withdrawal of the double patenting rejection are respectfully requested.

Claims 67, 68, 77-82 and 87-96 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over

- claims 1-9, 13-16, 18-51 and 64-65 of copending application No. 11/233,945;
- claims 1, 43-45 and 49-53 of copending Application No. 11/234,868;
- claims 26-29, 31, 32, 34-49 and 51-56 of copendidng Application No. 11/244,416;
- claims 1, 19-21, 32, 56-59 and 62 of copending Application No. 11/368,367; and
- claims 1-5 of copending Application 11/406,079

listed in paragraphs 29-34 of the Office Action. The rejections are respectfully traversed.

The Office Action indicated that although the rejections are provisional, the rejections cannot be held in abeyance. Applicants will address the provisional obviousness-type double

patenting rejections at the time allowable subject matter is determined in the present application, provided the allowable claims are still subject to the double patenting rejections.

Accordingly, reconsideration and withdrawal of the double patenting rejections are respectfully requested.

IV. THE REJECTIONS UNDER 35 U.S.C. §103 ARE OVERCOME

Claims 67, 68, 77-82 and 87-96 are rejected under 35 US.C. §103(a) as allegedly being unpatentable over Reed *et al.* (WO 93/05064). The rejection is respectfully traversed.

The Office Action states that Reed *et al.* teaches steroid sulphatase inhibitors such as oestrone-3-sulphamate and oestrone-3-N,N-dimethylsulphamate and their use in the treatment of estrogen-dependent cancers such as breast cancer. The Office Action further asserts that Reed *et al.* teaches the utilization of substituted oestrones such as 2-methoxy-estrone (page 4, line 35), which is described in the present invention. The Office Action concludes that it would have been obvious to utilize any of the species of the prior art, including 2-methoxy-estrone sulphamate, with the reasonable expectation that the compound would be useful in the inhibition of steroid sulphatase and in the treatment of breast cancer as taught by Reed *et al.* Applicants respectfully disagree.

Initially, in determining whether claims are obvious in view of a reference, it is well-settled that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski,* 12 US.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz,* 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further still, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch,* 23 US.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, for an obviousness rejection to stand, **both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure.** *In re Dow,* 5 u.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Furthermore, the Examiner is respectfully reminded that a species (or subgenus) may be patentably distinct from a genus. *See e.g., In re Baird,* 29 u.S.P.Q.2d 1550, 1551 (Fed. Cir.

1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."). *See also In re Jones,* 21 u.S.P.Q.2d 1941, 1943 (Fed. Cir. 1992) (rejecting Commissioner's argument that "regardless .. how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it").

Indeed, mention is also made of the Commentary to Rules of Practice, 49 Fed. Reg. 48416, 48433 (Dec. 12, 1984), 1050 O.G. 395 (Jan. 29, 1985), corrected to 50 Fed. Reg. 23122 (May 31, 1985), 1059 O.G. 27 (Oct. 22, 1985), which provides in pertinent part:
Thus, if a species is patentable over a genus, the species is a "separate patentable invention" from the genus. Compare *In re Taub,* 348 F.2d 556, 146 USPQ 384 (C.C.P.A., 1965).

In this regard, the Examiner's attention is also directed to *In re Sasse,* 207 U.S.P.Q. 107 (C.C.P.A. 1980), wherein the Court of Customs and Patent Appeals held that a claim to a genus and a claim to a species within the genus are not claims to the same or substantially the same subject matter in the sense of35 U.S.C. §135(b).

Establishing a *prima facie* case of obviousness requires that the prior art reference must teach or suggest all the claim limitations. The Examiner is respectfully reminded of the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. Furthermore, the Supreme Court has recently reaffirmed the factors set out in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18: "[T]he scope and content of the prior art are determined; differences between the prior art and the claims at issue are...ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727.

Reed *et al.* does not teach or suggest, *inter alia*, a method of inhibiting steroid sulphatase activity comprising administering a non-oestrogenic sulphamate compound.

Reed *et al.* teaches polycyclic compounds having a sulphamyl or substituted sulphamyl group, preferably at the 3-position. Although Reed *et al.* mentions that substituted polycyclic compounds, including 2-methoxy-estrone sulphamate, could be used in the invention, there is no teaching or suggestion in Reed *et al.* that would prompt one of skill in the art to select non-

oestrogenic oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H, as potent non-oestrogenic steroid sulphatase inhibitors, over any of the other compounds included in the genus taught by Reed *et al.* Furthermore, there is certainly nothing in Reed *et al.* that suggests that 2-methoxy-estrone sulphamate would have surprisingly superior properties such as having reduced oestrogenicity.

Applicants previously submitted a copy of Purohit *et al.* "The Development of A-ring Modified Analogues of Oestrone-3-O-sulphamate as Potent Steroid Sulphatase Inhibitors with Reduced Oestrogenicity," published in 1998. As described in Purohit, one of the problems in the art surround the use of standard steroid sulphatase inhibitors such as EMATE is that the compounds have a stimulatory effect on uterine growth. Such a stimulatory effect is undesirable in potential therapies for diseases such as cancer.

Surprisingly, it has now been found that the A-ring modified compounds of the present invention, having at least one additional substituent at one or more of the 2- and 4-positions, are vastly superior to previous steroid sulphatase inhibitors. Specifically, the A-ring modified compounds exhibit steroid sulphatase inhibition with significantly decreased estrogenicity when compared to compounds such as EMATE. For example, the Examiner's attention is respectfully directed to Figure 4 of Purohit *et al.*, which compares *in vivo* sulphatase activity following administration of 2- or 4-position substituted derivates or EMATE. The sulphatase activity measured following administration of compounds such as 4-Nitro EMATE, 2-Methoxy EMATE, and 4-n-Propyl EMATE was statistically similar to the activity levels measured following administration of EMATE. Furthermore, Figure 5 of Purohit *et al.* depicts the results of the uterine growth assay, which demonstrates that administration of A-ring derivate compounds resulted in little or no uterine growth, in contrast to the effects of the administration of EMATE.

Accordingly, the present invention is patentable over Reed *et al.* as there is no suggestion, motivation, or teaching in Reed *et al.* that would prompt one of skill in the art to select the compounds of the present invention from the numerous compounds of the genus described by Reed *et al.*

Moreover, the present invention is additionally patentable over Reed *et al.* as there is no suggestion, motivation, or teaching in Reed *et al.* that would convey to one of skill in the art that the compounds of the present invention are non-oestrogenic while being highly efficacious

steroid sulphatase inhibitors and therefore are surprisingly advantageous in treating endocrine-dependent tumors, in particular breast tumors. Furthermore, Reed *et al.* does not relate to a method comprising administering the presently claimed non-oestrogenic compounds to a patient in need of inhibition of steroid sulphatase or of treatment of endocrine-dependent cancer by a non-oestrogenic compound.

As such, the cited reference does not render the claimed invention *prima facie* obvious.

For all of these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) over Reed *et al.* are respectfully requested.

V. OTHER MATTERS

The Examiner alleges that "the finding that one of the prior art compound is more efficacious as compared to other is not unexpected or unobvious since the skilled artisan in the art would reasonably expect differences in potency of the prior art compounds". The Examiner further contends that "Reed teaches the ABCD ring of formula (II) can be 2-methoxy-estrone and, thus anticipates the use of the presently claimed compound".

Contrary to the Examiner's allegations, Applicants do not relate to minor variations in compound activity, but are pointing to the marked difference in oestrogenicity of the present compounds. By teaching that "ABCD ring of formula (II) can be 2-methoxy-estrone", Reed does not anticipate the use of the presently claimed compounds, as the reference does not teach or suggest that oestrone-3-sulphamate compounds having at least one other substituent at one or more of the 2- and 4-positions on the A-ring, wherein the 2- and 4-positions cannot be both H are potent non-oestrogenic steroid sulphatase inhibitors which can be administered to a patient in need of inhibition of steroid sulphatase or of treatment of endocrine-dependent cancer by a non-oestrogenic compound. Basically, even if Reed relates to 2-methoxy-estrone, one skilled in the art would not be able to predict that 2-nitro, or 2, 4-dinitro, or 4-nitro, or 2-alkyl, or 2,4-dialkyl or 4-alkyl or other 2- and/or 4-substituted oestrone-3-sulphamate compounds disclosed in the present claims are non-oestrogenic and can be used according to the present invention based on the teachings of Reed. Applicants respectfully submit that the Examiner's assertion that one skilled in the art can expect the compounds described by Reed to be non-oestrogenic is based on an improper hindsight.

As such, the cited reference does not render the claimed invention obvious.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) over Reed *et al.* are respectfully requested.